Hypoglycemia (low blood glucose):
Hypoglycemia is often called an "insulin reaction" or "low blood sugar". It may happen when you do not have enough sugar in your blood. Common causes of hypoglycemia are illness, emotional or physical stress, too much insulin, too little food or missed meals, and too much exercise or activity.

Early warning signs of hypoglycemia may be different, less noticeable or not noticeable at all in some people. That is why it is important to check your blood sugar

Hypoglycemia can happen with:

- **The wrong insulin dose.** This can happen when too much insulin is injected. For pump users it could happen if the pump dose is too high.
- **Not enough carbohydrate (sugar or starch) intake**. This can happen if
  - a meal or snack is missed or delayed
  - you are vomiting or have diarrhea that decreases the amount of sugar absorbed by your body
  - you drink alcohol
- **Medicines that affect insulin.** Be sure to discuss all your medicines with your healthcare provider. **Do not start any new medicines until you know how they may affect your insulin dose.**
- **Medical conditions that can affect your blood sugar levels or insulin.** These conditions include diseases of the adrenal glands, the pituitary, the thyroid gland, the liver, and the kidney.
- **Too much glucose use by the body.** This can happen if you exercise too much or have a fever.
- **Injecting insulin the wrong way or in the wrong**

Hypoglycemia can be mild to severe. Its onset may be rapid. Some patients have few or no warning symptoms, including:

- patients with diabetes for a long time
- patients with diabetic neuropathy (nerve problems)
- patients using certain medicines for high blood pressure or heart problems

Hypoglycemia may reduce your ability to drive a car or use mechanical equipment without chances of injury to yourself or others.

Severe hypoglycemia can be dangerous and can cause temporary or permanent harm to your heart or brain. **It may cause unconsciousness, seizures, or death.**

Symptoms of hypoglycemia may include:

- anxiety, irritability, restlessness, trouble concentrating, personality changes, mood changes, or other abnormal behavior
- tingling in your hands, feet, lips, or tongue
- dizziness, light-headedness, or drowsiness
- nightmares or trouble sleeping

- headache
- blurred vision
- slurred speech
- palpitations (fast heart beat)
- sweating
- tremor (shaking)
- unsteady gait (walking).

If you have hypoglycemia often or severe or it is hard for you to know if you have the symptoms of hypoglycemia, talk to your healthcare provider.

Mild to moderate hypoglycemia can be treated by eating or drinking carbohydrates such as (fruit juice, raisins, sugar candies, milk or glucose tablets). Talk to your healthcare provider about the amount of carbohydrates you should eat to treat mild to moderate hypoglycemia.

Severe hypoglycemia may require the help of another person or emergency medical people. Someone with hypoglycemia who cannot take foods or liquids with sugar by mouth needs medical help fast and will need treatment with a glucagon injection or glucose given intravenously (IV). Without medical help right away, serious reactions or even death could happen.

Hyperglycemia (high blood glucose):
Hyperglycemia occurs when you have too much sugar in your blood. Usually, it means there is not enough insulin to break down the food you eat into energy your body can use. Hyperglycemia can be caused by a fever, an infection, stress, eating more than you should, taking less insulin than prescribed, or it can mean your diabetes is getting worse.

Hyperglycemia can happen with:
- **The wrong insulin dose.** This can happen from:
  - injecting too little or no insulin
  - incorrect storage (freezing, excessive heat)
  - use after the expiration date.

  For pump users this can also be caused when the bolus dose of APIDRA infusion or the basal infusion is set too low, or the pump is delivering too little insulin.
- **Too much carbohydrate intake**. This can happen if you eat larger meals, eat more often or increase the amount of carbohydrate in your meals.
- **Medicines that affect insulin.** Be sure to discuss all your medicines with your healthcare provider. **Do not start any new medicines until you know how they may affect your insulin dose.**
- **Medical conditions that affect insulin**. These medical conditions include fevers, infections, heart attacks, and stress.
- **Injecting insulin the wrong way or in the wrong** ———————

Testing your blood or urine often will let you know if you have hyperglycemia. If your tests are often high, tell your healthcare provider so your dose of medicine can be changed.

Hyperglycemia can be mild or severe. It can **diabetic ketoacidosis (DKA)** **Unconsciousness and death**

Diabetic ketoacidosis occurs most often in patients with Type 1 diabetes. It can also happen in patients with Type 2 diabetes who become very sick.
Because some patients get few symptoms of hyperglycemia, it is important to check your blood sugar regularly.

Symptoms of hyperglycemia include:
- confusion or drowsiness
- increased thirst
- decreased appetite, nausea, or vomiting
- rapid heart rate
- increased urination and dehydration (too little fluid in your body).

Symptoms of DKA also include:
- fruity smelling breath
- fast, deep breathing
- stomach area (abdominal) pain.

Severe or continuing hyperglycemia or DKA needs evaluation and treatment right away by your healthcare provider.

Other possible side effects of APIDRA include:

Serious Allergic reactions:
Sometimes, severe, life-threatening allergic reactions can happen with insulin. If you think you are having a severe allergic reaction, get medical help right away. Signs of insulin allergy include:
- a sudden rash all over your body
- shortness of breath
- wheezing (trouble breathing)
- a fast pulse
- sweating
- low blood pressure.

Reactions at the injection site:
Injecting insulin can cause the following reactions on the skin at the injection site:
- a little depression in the skin (lipoatrophy)
- skin thickening (lipohypertrophy)
- red, swelling, itchy skin (injection site reaction).

You can reduce the chance of getting an injection site reaction if you change (rotate) the injection site each time. An injection site reaction should clear up in a few days or a few weeks. If injection site reactions do not go away or keep happening, call your healthcare provider.

Tell your healthcare provider if you have any side effects that bother you.

These are not all the side effects of APIDRA. Ask your healthcare provider or pharmacist for more information.

How should I store APIDRA?

- **Unopened vial:** Store new unopened APIDRA vials in the refrigerator (not the freezer) between 36°F to 46°F (2°C to 8°C). Do not freeze APIDRA. Keep APIDRA out of direct heat and light. If a vial freezes or overheats, discard it.
- **Open (In Use) vial**: Once a vial is opened, you can keep it in the refrigerator or as cool as possible (below 77°F [25°C]), but the opened vial must be used within 28 days. If refrigeration is not possible, the open vial in use can be kept unrefrigerated for up to 28 days away from direct heat and light, as long as the temperature is not greater than 77°F (25°C). For example, do not leave it in your car on a summer day.
- **Insulin pump infusion sets:** Infusion sets (reservoirs, tubing, and catheters) and the APIDRA in the reservoir should be thrown away:
    - after no more than 48 hours of use or
    - after exposure to temperatures higher than 98.6°F (37°C).
- Do not use a vial of APIDRA after the expiration date stamped on the label.
- Do not use APIDRA if it is cloudy or if you see particles.

General Information about APIDRA

Use APIDRA only to treat your diabetes. **Do not** give or share APIDRA with another person, even if they have diabetes also. It may harm them.

This leaflet summarizes the most important information about APIDRA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about APIDRA that is written for health professionals. For more information about APIDRA call 1-800-633-1610 ***[DSRCS Comment: List sponsor website, if available.]***.

What are the ingredients in APIDRA?

Active Ingredient: insulin glulisine

Inactive Ingredients: m-cresol, trometamol, sodium chloride, polysorbate 20, and water for injection.

Instructions for Use

How do I draw the insulin into the syringe?

- **The syringe must be new and not contain any other medicine.**
- **Do not mix APIDRA with any other type of insulin than NPH.** If you are mixing APIDRA with NPH human insulin, draw APIDRA into the syringe first. Inject the mixture right away.

Follow these steps:

1. Wash your hands.
2. Check the insulin to make sure it is clear and colorless. Do not use it after the expiration date or if it is cloudy or if you see particles.
3. If you are using a new vial, remove the protective cap. **Do not** remove the stopper.
4. Wipe the top of the vial with an alcohol swab. You do not have to shake the vial of APIDRA before use.
5. Use a new needle and syringe every time you take a dose. Use disposable syringes and needles only once. Throw them away properly. **Never** share needles and syringes.
6. Draw air into the syringe equal to your insulin dose. Put the needle through the rubber top of the vial and push the plunger to inject the air into the vial.
7. Leave the syringe in the vial and turn both upside down. Hold the syringe and vial firmly in one hand.
8. Make sure the tip of the needle is in the insulin. With your free hand, pull the plunger to withdraw the correct dose into the syringe.
9. Before you take the needle out of the vial, check the syringe for air bubbles. If bubbles are in the syringe, hold the syringe straight up and tap the side of the syringe until the bubbles float to the top. Push the bubbles out with the plunger and draw insulin back in until you have the correct dose. If you are mixing APIDRA with NPH insulin check with your healthcare professional on how to mix.
10. Remove the needle from the vial. Do not let the needle touch anything. You are now ready to inject.

How do I inject APIDRA?

Inject APIDRA under your skin. Take APIDRA as prescribed by your healthcare provider.

You should look at the medicine in the vial. If the medicine is cloudy or has particles in it, do not use it. Contact your healthcare provider. Use a new vial.

Follow these steps:

1. Decide on an injection area - either upper arm, thigh or abdomen. Injection sites within an injection area must be different from one injection to the next.
2. Use alcohol or soap and water to clean the skin where you are going to inject. The injection site should be dry before you inject.
3. Pinch the skin. Stick the needle in the way your healthcare provider showed you. Release the skin.

4. Slowly push in the plunger of the syringe all the way, making sure you have injected all the insulin. Leave the needle in the skin for about 10 seconds. Pull the needle straight out and gently press on the spot where you injected yourself for several seconds. **Do not rub the area.**

5. Follow your healthcare provider's instructions for throwing away the needle and syringe. Do not recap the syringe. Used needle and syringe should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.

How should I infuse APIDRA with an external subcutaneous insulin infusion pump?

Do not mix APIDRA with any other insulin or liquid when used in a pump.

- APIDRA is recommended for use in the following pumps and infusion sets: Disetronic® H-Tron® plus V100 and D-Tron® with Disetronic catheters (Rapid™, Rapid C™, Rapid D™, and Tender™); MiniMed® Models 506, 507, 507c and 508 with MiniMed catheters (Sof-set Ultimate QR™, and Quick-set™)‡. Refer to the instruction manual of your specific pump on proper use of insulin in a pump. Call your healthcare provider if you have questions about using the pump.

- If the pump or infusion set does not work right you may not receive the right dose of insulin. Hypoglycemia, hyperglycemia or ketosis can happen. Problems should be identified and corrected as quickly as possible. Because APIDRA starts working faster and does not work as long, you may have less time to identify and correct the problem than with regular insulin.

- If you start using APIDRA by pump infusion, you may need to adjust your insulin doses. Check with your healthcare provider.

- You must use insulin from a new vial of APIDRA if unexplained hyperglycemia happens, or if pump alarms do not respond to all of the following:
  - a repeat dose (injection or bolus) of APIDRA
  - a change in the infusion set, including the reservoir with APIDRA
  - a change in the infusion site.

If these actions do not work, you may need to restart your injections with syringes and you must call your healthcare provider. Continue to check your blood sugar often.

The infusion set, reservoir with insulin, and infusion site should be changed:
- every 48 hours or less
- when unexpected hyperglycemia or ketosis occurs
- when alarms sound, as specified by your pump manual
- if the insulin has been exposed to temperatures over 98.6°F (37°C). If the insulin or pump could have absorbed radiant heat, for example from sunlight, that would heat the insulin

to over 98.6°F (37°C). Dark colored pump cases or sport covers can increase this type of heat. The location where the pump is worn may affect the temperature.

- Patients who get skin reactions at the infusion site may need to change infusion sites more often.

ADDITIONAL INFORMATION

DIABETES FORECAST is a national magazine designed especially for patients with diabetes and their families and is available by subscription from the American Diabetes Association, National Service Center, 1701 N. Beauregard Street, Alexandria, Virginia 22311, 1-800-DIABETES (1-800-342-2383). You may also visit the ADA website at www.diabetes.org.

Another publication, **DIABETES COUNTDOWN**, is available from the Juvenile Diabetes Research Foundation International (JDRF), 120 Wall Street, 19th Floor, New York, New York 10005, 1-800-JDF-CURE (1-800-533-2873). You may also visit the JDRF website at www.jdf.org.

To get more information about diabetes, check with your healthcare professional or diabetes educator or visit www.DiabetesWatch.com. Rev. XXXX

Aventis Pharmaceuticals Inc.
Kansas City, MO 64137 USA

† Lantus® is a trademark of Aventis Pharmaceuticals Inc.

‡ The brands listed are the registered trademarks of their respective owners and are not trademarks of Aventis Pharmaceuticals, Inc.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jeanine Best
1/15/04 01:11:04 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
1/15/04 04:29:06 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

January 14, 2004

Dr. David Orloff
Director, Division of Metabolic and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

NDA 21-629: APIDRA™
HMR 1964 – Insulin glulisine (rDNA human insulin analog)
Response to CMC reviewer request for information
regarding APIDRA™ NDA submission

Dear Dr. Orloff:

Reference is made to the above-mentioned New Drug Application (NDA) for APIDRA™ (HMR 1964 – insulin glulisine), which was submitted to the Agency on June 18, 2003. On December 23, 2003, CMC Reviewer Dr. Xavier Ysern contacted Aventis Pharmaceuticals, Inc. and requested information regarding the most recent inspections from any national regulatory agency for the following two drug substance testing facilities identified in the APIDRA™ NDA:

In a follow-up phone conversation on January 8, 2004 with Gary Ruezinsky (Regulatory CMC, Aventis Pharmaceuticals), the requested information was verbally given to Dr. Ysern.

The purpose of this January 14, 2004 correspondence is to *officially* submit the response to the information request of Dr. Ysern. Our response has been provided electronically on the enclosed CD and can be found within the CMC *"substan"* folder. Aventis certifies that all electronic media have been scanned and found to be free of any known computer viruses (Symantec Norton Anti-Virus, Version 7.50.846, current 60107d 1/7/2004, Scan Engine 4.1.0.6.).

We consider the filing of the original New Drug Application for APIDRA™ to be a confidential matter, and request that the Food and Drug Administration make neither its content, nor any future communications in regard to it, public without first obtaining the written permission of Aventis Pharmaceuticals, Inc.

Aventis Pharmaceuticals Inc. looks forward to working with the Division to facilitate the review of the APIDRA™ NDA. Should you have any questions regarding this material, please contact the undersigned by telephone at (908) 231-3536 or by fax at (908) 304-6318 or, in my absence, please contact Steve Caffé, M.D. by telephone at (908) 231-5863.

Sincerely,

Odile Ernoux, M.D.
Director, Regulatory Affairs
Aventis Pharmaceuticals, Inc.
Phone: (908)-231-3536
Fax: (908)-304-6318

__6__ page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

(b4)

A-6

Shari L. Targum, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852
Tel (301) 594-5377, FAX (301) 594-5494

Memorandum

DATE: December 22, 2003

FROM: Shari L. Targum, M.D., Medical Officer
Division of Cardio-Renal Drug Products, HFD-110

THROUGH:
Norman Stockbridge, M.D., Ph.D., Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Douglas C. Throckmorton, M.D., Director, Division of Cardio-Renal Drug Products, HFD-110

TO: Joanna K. Zawadski, M.D., Medical Officer,
Division of Endocrine and Metabolic Drug Products, HFD- 510
H. Julie Rhee, Project Manager, Division of Endocrine and Metabolic Drug Products, HFD-510

SUBJECT: Review of treatment-emergent cardiac disorders in NDA #21,629

NAME OF DRUG: insulin glulisine
TRADE NAME: Apidra
FORMULATION: injectable
RELATED APPLICATIONS: N/A
APPROVED INDICATIONS: N/A
SPONSOR: Aventis Pharmaceuticals

DOCUMENTS AVAILABLE FOR REVIEW: 1. Medical Officer consultation request; 2. NDA 21,629 (electronic document room: received 6/18/03); 3. NDA 21-629: 120-Day Safety Update (electronic document room: received 11/4/03).

DATE CONSULT RECEIVED: October 8, 2003
DATE CONSULT COMPLETED: December 22, 2003

BACKGROUND & RATIONALE:
Insulin glulisine is a third rapid-acting insulin analog submitted for approval for use in Type 1 and 2 diabetes. The other two rapid-acting insulin analogs (Humalog (lispro); NDA 20,563 and NovoLog (aspart); NDA 20, 986) were approved on 6/14/96 and 6/7/00, respectively.

The current NDA submission for glulisine consists of data from four Phase 3 open-label, multinational, randomized, controlled, parallel-group, active-controlled studies. Due to the nature of the disease/treatment, none of the Phase 3 studies involved a placebo control group . Two of these studies (3001 and 3002) were 26-week studies and the other two (3004 and 3006) were 12-week studies. Three studies (3001, 3004 and 3006) were performed in Type 1 patients, and one study (3002) was completed in Type 2 patients. In one 26-week study (3001) comparing glulisine and lispro in adults with Type 1 diabetes mellitus, there was a 9-fold increase in treatment-emergent cardiac disorders (i.e, 9/339 [2.7%] in

glulisine-treated patients vs. 1/333 [0.3%] in the lispro-treated patients). No increase in number of cardiac events was noted in the 26-week study in Type 2 patients.
Data from Study 3005, another 26-week study in Type 2 diabetics, as well as data from two extension studies (3011 and 3012) were not included in the NDA but were scheduled to be submitted in the 120-day Safety Update.

We have been asked if the observed emergent cardiac events in the Type 1 diabetes mellitus patients treated with glulisine in NDA 21,629 are related to treatment with the drug. In addition, we have been asked to comment on a QT study in the NDA.

Glulisine: Glulisine, a recombinant rapid-acting insulin analog, differs from human insulin by the replacement of asparagine in position B3 by lysine, and lysine at position B29 by glutamic acid. According to the sponsor, glulisine's time-action profile define it as a member of the rapid-acting insulin subfamily of short-acting insulin preparations (other rapid-acting insulin preparations include lispro and aspart). The sponsor has suggested that glulisine can be given subcutaneously 0-15 minutes before or immediately following a meal in order to provide safe and effective postprandial glucose control. The target indication for glulisine is the treatment of diabetes mellitus.

Table 1. Phase III Efficacy Studies: glulisine (original submission)

Study #	Objective	Study design	# treated	Diagnosis	Duration of Treatment	Study status
3001	Efficacy/ safety	Multicenter, open randomized, active-control, parallel-group	Total: 672 Glulisine: 339 Lispro: 333	Type 1 DM	26 weeks	Completed
3002	Efficacy/ safety	Multicenter, open randomized, active-control, parallel-group	Total: 876 Glulisine: 435 Regular insulin: 441	Type 2 DM	26 weeks	Completed
3004	Efficacy/ safety postmeal vs. premeal (vs. insulin)	Multicenter, open, randomized, active-control, parallel-group	Total: 860 Premeal glulisine: 286 Postmeal glulisine: 296 Regular insulin: 278	Type 1 DM	12 weeks	Completed
3006	Safety/compatibility when used in external pumps (continuous subcut infusion)	Multicenter, open, randomized, active-control, parallel-group,	Total: 59 Glulisine: 29 Aspart: 30	Type 1 DM	12 weeks	Completed
3005	Efficacy/ safety	Multicenter, open, randomized, active-control, parallel-group	Number treated: 890	Type 2 DM	26 weeks	Data in Safety Update
3011	1-year safety, compare efficacy (6 month extension--3001)	Multicenter, open, active- control, parallel-group	Number treated: 589	Type 1 DM	26 weeks	Data in Safety Update
3012	1-year safety, compare efficacy (6 month extension--3002)	Multicenter, open, active-control, parallel-group	Number treated: 709	Type 2 DM	26 weeks	Data in safety update

Dosing for each drug was titrated based on 2 hour postprandial blood glucose with different regimens according to the particular study. Patients were stratified by prior insulin or oral hypoglycemic use.

This reviewer will proceed from the "general to the specific," considering the overall cardiovascular safety results and then the safety results from Study 3001.

Overall Exposure:
Exposure is listed in the next two tables (original submission and 120-day safety update) below.

Table 2. Overall Exposure: original submission (No. subjects who received ≥ 1 dose study treatment)

	No. Studies	Total	Glulisine	Comparator
Adult clinical pharmacology studies	13	228	212	193
Pediatric clinical pharmacology study	1	20	20	20
Completed Phase III studies	4	2467	1385	1082
Adults with type 1 DM	3	1591	950	641
Adults with type 2 DM	1	876	435	441
Total exposed in completed studies	18	2715	1617	1295
Ongoing or completed/not reported Phase III studies:				
Adults with type 1 DM (3011)	1	589	NA	NA
Adults with type 2 DM (3005)	1	675	NA	NA
Adults with type 2 DM (3012)	1	711	NA	NA

Source: Sponsor: Clinical Overview Table 1.

Table 3 – 120 day safety update: Numbers of adult subjects who received one or more doses of study treatment (Phase III studies)

		No. subjects treated		
	No. studies	**Total**	**Glulisine**	**Comparators**
Subjects with type 1 diabetes	3 (+ 1 extension)	1591	950	641
Study 3001/3011	–	672	339	333
(Study 3011) [a]		(589)	(302)	(287)
Study 3004	–	860	582	278
Study 3006	–	59	29	30
Subjects with type 2 diabetes	2 (+ 1 extension)	1766	883	883
Study 3002/3012	–	876	435	441
(Study 3012) [a]		(709)	(357)	(352)
Study 3005	–	890	448	442
Total exposed Phase III	5 (+ 2 extensions)	3357	1833	1524
Total exposed Phase I + III [b]	18 (+ 2 extensions)	3585	2045	1717

[a] Subjects enrolled in the 3011 or 3012 extension study were previously treated in Study 3001 or 3002, respectively, and are therefore not counted in the sums of subjects treated.

[b] Includes 228 adult subjects (212 who received glulisine and 193 who received one or more comparator) treated in 13 clinical pharmacology studies. Subjects who participated in more than one clinical pharmacology study of glulisine or who received more than one comparator in these studies are included only once. For more details, see the Summary of Clinical Safety, Section 1.2.1.

In the 120-day safety update, about 300 type 1 DM patients were treated with glulisine for ≥ 26 weeks as seen in the next table. **Reviewer's comment**: From a cardiovascular safety point of view, this is a small database for long-term exposure in type 1 DM.

Table 4 : Duration of exposure to glulisine (Studies 3001/3011, 3002/3012, 3004, 3005, and 3006): safety update

	No. subjects treated with glulisine			
Treatment duration:	≥≥1 day	≥≥12 weeks	≥≥26 weeks	≥≥52 weeks
All adult subjects (Phase I + III) [a]	2045	1572	1054	436
All subjects (Phase III)	1833	1572	1054	436
Subjects with type 1 diabetes	950	728	318	209
Subjects with type 2 diabetes	883	844	736	227

[a] Includes 212 adult glulisine subjects treated in one or more 13 clinical pharmacology studies.
Subjects who participated in more than one study of glulisine are counted only once.

Demographic information is shown below. Except for geographic variation (type 1 DM), there appear to be no imbalances between glulisine and comparators.

Table 5 : Demographics and other background characteristics: safety update (Studies 3001/3011, 3002/3012, 3004, 3005, and 3006) (ITT population)

		Type 1 diabetes			Type 2 diabetes		All studies	
		Glulisine		Comparators	Glulisine	Comparators	Glulisine	Comparators
No. ITT subjects		950		641	883	883	1833	1524
Geographical region								
North America	n (%)	492	(51.8)	235 (36.7)	377 (42.7)	374 (42.4)	869 (47.4)	609 (40.0)
Europe	n (%)	327	(34.4)	325 (50.7)	184 (20.8)	175 (19.8)	511 (27.9)	500 (32.8)
Australia	n (%)	90	(9.5)	43 (6.7)	84 (9.5)	91 (10.3)	174 (9.5)	134 (8.8)
South Africa	n (%)	41	(4.3)	38 (5.9)	53 (6.0)	56 (6.3)	94 (5.1)	94 (6.2)
Sex								
Male	n (%)	525 (55.3)		342 (53.4)	460 (52.1)	445 (50.4)	985 (53.7)	787 (51.6)
Female	n (%)	425 (44.7)		299 (46.6)	423 (47.9)	438 (49.6)	848 (46.3)	737 (48.4)
Age (years)								
Mean (SD)		40.0 (11.91)		39.3 (12.09)	59.4 (9.65)	58.8 (9.81)	49.3 (14.54)	50.6 (14.49)
≥65	n (%)	20	(2.1)	14 (2.2)	254 (28.8)	271 (30.7)	274 (14.9)	285 (18.7)
≥75	n (%)	.	–	–	49 (5.5)	30 (3.4)	49 (2.7)	30 (2.0)
BMI (kg/m²)								
Mean (SD)		26.33 (4.285)		25.91 (4.344)	33.01(6.261)	32.73 (6.288)	29.55 (6.290)	29.86 (6.492)
BMI >28	n (%)	281 (29.6)		176 (27.5)	689 (78.0)	681 (77.1)	970 (52.9)	857 (56.2)
Race								
White	n (%)	910	(95.8)	609 (95.0)	777 (88.0)	786 (89.0)	1687 (92.0)	1395 (91.5)
Black	n (%)	12	(1.3)	12 (1.9)	66 (7.5)	62 (7.0)	78 (4.3)	74 (4.9)
Asian/Oriental	n (%)	10	(1.1)	8 (1.2)	21 (2.4)	20 (2.3)	31 (1.7)	28 (1.8)
Multiracial	n (%)	18	(1.9)	12 (1.9)	19 (2.2)	15 (1.7)	37 (2.0)	27 (1.8)
Hispanic ethnicity [a]	n (%)	21 (2.2)		11 (1.7)	68 (7.7)	70 (7.9)	89 (4.9)	81 (5.3)

[a] Data collected in Studies 3002/3012, 3004, and 3005 only, independently of race (a subject with Hispanic ethnicity was also assigned to
any one category of race).
Data presented for Studies 3001/3011 and 3002/3012 are for the baseline visit of Study 3001 and 3002, respectively.
Note on comparators: Type 1 diabetes: Study 3001/3011 (comparator lispro), Study 3004 (comparator regular insulin), Study 3006 (comparator aspart); type 2 diabetes: Study 3002/3012 (comparator regular insulin), Study 3005 (comparator regular insulin).

Table 6: Summary of all TEAEs by system organ class: cardiac disorders: type 1 diabetes pooled (Studies 3001/3011, 3004, and 3006): safety update

			No. (%) subjects							
System organ class	Glulisine		All comparators		Lispro		Regular		Aspart	
Total no. ITT subjects	950	(100)	641	(100)	333	(100)	278	(100)	30	(100)
Total with 1 or more TEAE	629	(66.2)	423	(66.0)	229	(68.8)	174	(62.6)	20	(66.7)
Cardiac disorders	15	(1.6)	4	(0.6)	2	(0.6)	1	(0.4)	1	(3.3)

Note on comparators: lispro (Study 3001/3011), regular insulin (Study 3004), aspart (Study 3006).

No imbalance was seen in the pooled type 2 DM where the incidence of cardiac events was 6.9% in glulisine as well as comparator.

Deaths: No deaths were reported in the clinical pharmacology studies. In the completed Phase III studies (original submission), 3 deaths were noted in Study 3002. The causes of these deaths were: GI hemorrhage with shock and subsequent MI (1 glulisine subject) and cardiac arrest (2 insulin subjects). A summary of deaths listed in the 120-day safety update is presented in the table below:

Table 7: Subject listing of all deaths: safety update

Study	Investigator/ Subject	Age/ Sex	Last day on study med./ Day of death	Primary cause of death [a] (Adverse event preferred term)
Treatment: glulisine				
3002	0214/20 [b]	77/M	27/28	Digestive hemorrhage shock (myocardial infarction, shock hemorrhagic)
3011	1303/06 [c]	50/M	338/340	Asystole (diabetic ketoacidosis, cardiac arrest)
3012	0143/24 [c]	70/M	191/195	Subdural hematoma (brain herniation, subdural hematoma, respiratory arrest)
3005	0351/03 [c]	87/M	84/85	Hemorrhagic intracerebral/ intraventricular accident (cerebral hemorrhage)
3005	0965/10	42/F	35/36	Bleeding of esophageal varices (esophageal varices hemorrhage)
Treatment: regular insulin				
3002	0308/07 [b]	59/F	55/56	Cardiac arrest (cardiac arrest)
3002	0309/02 [b]	67/M	43/44	Heart attack (cardiac arrest)
3012	0128/18 [c]	67/M	256/258	Massive pulmonary embolus (pulmonary embolism)
3012	0214/18	64/M	312/332	Gastric ulcer perforation (gastric ulcer perforation)
3005	2159/10 [c]	61/F	20/20	Aspiration (aspiration)

Subject age is on entry into the study.

[a] Primary cause of death according to the investigator's assessment. The adverse event preferred terms shown are those with an outcome of death.

[b] Previously reported in the original NDA submission, based on a final study database.

[c] Previously reported in the original NDA submission, based on a preliminary study database or Pharmacovigilance reporting. Some

information may have been updated in the current document.

Reviewer comment: This reviewer cannot tell if the hemorrhagic events (different sites) in the glulisine group represent some type of underlying drug effect, or bleeding diathesis, or represent "noise."

Table 8: Summary of all serious cardiac TEAEs in ≥≥0.5% of subjects in any pooled treatment group (Studies 3001/3011, 3002/3012, 3004, 3005, and 3006): safety update

	No. (%) subjects					
	Type 1 diabetes		Type 2 diabetes		All studies	
System organ class/ Preferred term	Glulisine	Comparators	Glulisine	Comparators	Glulisine	Comparators
Total no. ITT subjects	950 (100)	641 (100)	883 (100)	883 (100)	1833 (100)	1524 (100)
Total with serious TEAEs	137 (14.4)	94 (14.7)	136 (15.4)	131 (14.8)	273 (14.9)	225 (14.8)
Cardiac disorders	8 (0.8)	1 (0.2)	30 (3.4)	36 (4.1)	38 (2.1)	37 (2.4)
Myocardial infarction	1 (0.1)	–	8 (0.9)	6 (0.7)	9 (0.5)	6 (0.4)
Coronary artery disease NOS	3 (0.3)	–	5 (0.6)	4 (0.5)	8 (0.4)	4 (0.3)
Angina pectoris	1 (0.1)	–	5 (0.6)	7 (0.8)	6 (0.3)	7 (0.5)
Angina unstable	–	–	3 (0.3)	6 (0.7)	3 (0.2)	6 (0.4)
Atrial fibrillation	–	–	1 (0.1)	4 (0.5)	1 (0.1)	4 (0.3)

Table includes preferred terms in ≥0.5% of subjects in any pooled treatment group (type 1 diabetes, type 2 diabetes, or all studies).
Note on comparators: Type 1 diabetes: Study 3001/3011 (comparator lispro), Study 3004 (comparator regular insulin), Study 3006 (comparator aspart); type 2 diabetes: Study 3002/3012 (comparator regular insulin), Study 3005 (comparator regular insulin).

Table 9: Summary of TEAEs reported as cardiac disorders in >1 subject in any treatment group: type 1 and 2 diabetes (Studies 3001/3011, 3002/3012, 3004, 3005, and 3006): safety update

	No. (%) subjects									
	Type 1 diabetes		Type 2 diabetes				All studies			
Preferred term name	Glulisine	Comparators	Glulisine		Comparators		Glulisine		Comparators	
Total no. ITT subjects	950 (100)	641 (100)	883	(100)	883	(100)	1833	(100)	1524	(100)
Total with cardiac disorder TEAEs	15 (1.6)	4 (0.6)	61	(6.9)	61	(6.9)	76	(4.1)	65	(4.3)
Angina pectoris	2 (0.2)	1 (0.2)	12	(1.4)	14	(1.6)	14	(0.8)	15	(1.0)
Coronary artery disease NOS	3 (0.3)	–	10	(1.1)	4	(0.5)	13	(0.7)	4	(0.3)
Myocardial infarction	1 (0.1)	–	8	(0.9)	6	(0.7)	9	(0.5)	6	(0.4)
Palpitations	2 (0.2)	–	7	(0.8)	2	(0.2)	9	(0.5)	2	(0.1)
Atrial fibrillation	1 (0.1)	–	5	(0.6)	9	(1.0)	6	(0.3)	9	(0.6)
Tachycardia NOS	2 (0.2)	–	4	(0.5)		–	6	(0.3)		–
Cardiac failure congestive	–	–	5	(0.6)	7	(0.8)	5	(0.3)	7	(0.5)
Bradycardia NOS	–	–	5	(0.6)	2	(0.2)	5	(0.3)	2	(0.1)
Acute myocardial infarction	3 (0.3)	–	2	(0.2)	1	(0.1)	5	(0.3)	1	(0.1)
Angina unstable	–	1 (0.2)	4	(0.5)	8	(0.9)	4	(0.2)	9	(0.6)
Sinus tachycardia	2 (0.2)	–	2	(0.2)		–	4	(0.2)		–
Coronary artery disease aggravated	–	1 (0.2)	3	(0.3)	4	(0.5)	3	(0.2)	5	(0.3)

Arrhythmia NOS	–	–	3	(0.3)	2	(0.2)	3	(0.2)	2	(0.1)
Ventricular extrasystoles	2 (0.2)	–	1	(0.1)	2	(0.2)	3	(0.2)	2	(0.1)
Cardiomegaly NOS	–	–	3	(0.3)		–	3	(0.2)		–
Myocardial ischemia	–	–	2	(0.2)	3	(0.3)	2	(0.1)	3	(0.2)
Acute coronary syndrome	–	–	2	(0.2)	2	(0.2)	2	(0.1)	2	(0.1)
Atrioventricular block first degree	–	–	2	(0.2)	1	(0.1)	2	(0.1)	1	(0.1)
Cardiac failure NOS	–	–	2	(0.2)	1	(0.1)	2	(0.1)	1	(0.1)
Sinus bradycardia	–	–	2	(0.2)		–	2	(0.1)		–
Congestive cardiac failure aggravated	–	–	1	(0.1)	3	(0.3)	1	(0.1)	3	(0.2)
Cardiac arrest	–	–	1	(0.1)	2	(0.2)	1	(0.1)	2	(0.1)
Ventricular hypertrophy	–	–	1	(0.1)	2	(0.2)	1	(0.1)	2	(0.1)
Coronary artery atherosclerosis	–	–		–	3	(0.3)		–	3	(0.2)
Ventricular tachycardia	–	–		–	2	(0.2)		–	2	(0.1)

Table includes preferred terms in >1 subject in any treatment group (type 1 diabetes, type 2 diabetes, or all studies).
TEAEs are sorted by decreasing frequency in glulisine subjects in all studies pooled.

Note on comparators: Type 1 diabetes: Study 3001/3011 (comparator lispro), Study 3004 (comparator regular insulin), Study 3006 (comparator aspart); type 2 diabetes: Study 3002/3012 (comparator regular insulin), Study 3005 (comparator regular insulin).

Withdrawals due to cardiovascular AE:

One glulisine subject in adult clinical pharmacology studies experienced a non-cardiovascular (acute bronchitis) TEAE resulting in discontinuation from study treatment.

In the Phase III studies (original submission), 14 (1.0%) glulisine and 13 (1.2%) comparator patients discontinued due to TEAE; five (0.4%) glulisine (2 patients with MI) and 1 (0.1%) comparator patients (MI) discontinued due to cardiac disorders.

Cardiac events by study (type 1 DM): A numerical imbalance in cardiac events appears in Study 3001; while an apparent trend appears in Study 3004, the total sample size on glulisine is larger than the comparator and the incidence rates are not significantly different. According to the sponsor, the imbalance in cardiac events appear to be driven by the results in Study 3001 (see next table).

Table 34 – Summary of all TEAEs reported as cardiac disorders: type 1 diabetes by study (Studies 3001, 3004, and 3006 by study)

	No. (%) subjects					
	Study 3001		Study 3004		Study 3006	
Preferred term name	Glulisine	Lispro	Glulisine	Regular	Glulisine	Aspart
Total no. ITT subjects	339 (100)	333 (100)	582 (100)	278 (100)	29 (100)	30 (100)
Total with cardiac disorder TEAEs	9 (2.7)	1 (0.3)	5 (0.9)	1 (0.4)	–	1 (3.3)
Acute MI	2 (0.6)	–	1 (0.2)	–	–	–
Coronary artery disease NOS	2 (0.6)	–	1 (0.2)	–	–	–
Angina pectoris	2 (0.6)	–	–	–	–	–
Tachycardia NOS	2 (0.6)	–	–			
Palpitations	1 (0.3)	–	1 (0.2)	–	–	–
Sinus tachycardia	–	–	2 (0.3)	–	–	–
Ventricular extrasystoles	–	–	2 (0.3)	–	–	–
Cardiac disorder NOS	1 (0.3)	–	–	–	–	–
Myocarditis NOS	1 (0.3)	–	–	–	–	–
Atrial fibrillation	–	–	1 (0.2)	–	–	–
MI	–	–	1 (0.2)	–	–	–
Angina unstable	–	–	–	1 (0.4)	–	–
Mitral valve collapse	–	1 (0.3)	–	–	–	–
Coronary artery disease aggravated	–	–	–	–	–	1 (3.3)

TEAEs are sorted by decreasing frequency in glulisine subjects.
Table S-82

Study 3001:

Study Summary: This was a 26-week, open, 1:1 randomized active-control parallel-group trial comparing glulisine with insulin lispro injected subcutaneously in patients with type 1 DM also using insulin glargine[1]. The primary objective was to demonstrate noninferiority of glulisine compared to lispro in the change from baseline to endpoint in GHb and to compare safety (adverse events, chemistry, lipids, hematology, E. coli protein antibodies) of glulisine with lispro. Secondary objectives included change in GHb at weeks 12 and 26, blood glucose parameters, symptomatic hypoglycemia, insulin doses and treatment satisfaction. A 26-week safety extension study was planned for completers of study 3001. The patient population included men and women $\geq$ 18 years old with type 1 DM (onset of diabetes under age 40 and requiring continuous insulin since diagnosis) with more than 1 year of continuous insulin treatment, BMI < 35 kg/m2 and HbA1c 6.0-11.0%. The primary analysis population was the intent-to-treat population; the per-protocol (PP) analysis was used to check for consistency of results.

Results:

Patient Disposition: A total of 772 patients entered the screening phase, of which 683 were randomized and 672 received study medication. Twenty-three patients (10 glulisine; 13 lispro) were withdrawn after the start of treatment. The ITT population, defined at patients randomized and treated, consisted of 672 patients (339 glulisine; 333 lispro). The PP population, defined as the ITT population excluding patients with a major protocol violation, consisted of 622 patients (315 glulisine; 307 lispro).

Baseline characteristics:

Baseline characteristics, including diabetic history and diabetic complications, follow in the next tables. According to the sponsor, glulisine patients had a duration of diabetes and insulin treatment of about 2 years longer than the lispro patients. At baseline, ongoing hypertension was noted in 70 (20.6%) of glulisine patients compared to 56 (16.8%) of lispro patients and 33.6% of glulisine patients reported the use of cardiovascular medications compared to 24.6% of lispro patients. Twenty (5.9%) glulisine patients and 16 (4.8%) lispro patients reported previous cardiovascular disease and 15 (4.4%) glulisine and 11 (3.3%) lispro patients reported ongoing cardiovascular disease at study entry. Concomitant

[1] Glargine is a basal insulin given once daily.

cardiovascular medications during the study were used by 120 (35.4%) glulisine and 83 (24.9%) lispro patients.
(Reviewer comment: A higher percentage of patients used cardiovascular medication than those actually reporting cardiovascular disease).

No imbalances were seen with regard to gender distribution (about 57-58% male), mean age (about 38 years), race (about 96-97% White), or mean BMI (about 25 kg/m^2). Baseline imbalances were seen with regard to time since diagnosis of diabetes, duration of insulin treatment (see below), history of diabetic retinopathy and neuropathy, history of hypertension, and baseline systolic BP (below)

Table 10: Diabetic history (ITT population)

Variable	Glulisine	Lispro	p-value
	(N = 339)	(N = 333)	
Mean (SD) time since diagnosis of diabetes (yrs)	17.4 (10.90)	15.6 (10.25)	0.0140
Mean (SD) age at diagnosis of diabetes (yrs)	21.9 (11.55)	22.5 (12.02)	0.4279
Mean (SD) duration of previous insulin treatment (yrs)	17.1 (10.86)	15.3 (10.27)	0.0183

N = number of subjects for whom data were available.

Table 11: History of diabetic late complications (ITT population)

Complication	Number (%) of subjects			
	Glulisine		Lispro	
Total number of ITT subjects	339 (100.0)		333 (100.0)	
Number of subjects with at least 1 complication	131	(38.6)	115	(34.5)
Diabetic retinopathy	109	(32.2)	89	(26.7)
Photocoagulation performed	51	(15.0)	36	(10.8)
Diabetic neuropathy	54	(15.9)	36	(10.8)
Autonomic neuropathy	12	(3.5)	5	(1.5)
Diabetic nephropathy	26	(7.7)	24	(7.2)
Diabetic macroangiopathy	13	(3.8)	7	(2.1)
Other	13	(3.8)	17	(5.1)

There was a slightly increased incidence in history of diabetic retinopathy and neuropathy[2] in the glulisine group compared to the lispro group.

In response to reviewer questions, the sponsor submitted the following additional information:

APPEARS THIS WAY
ON ORIGINAL

[2] The presence of autonomic neuropathy was determined by clinical history obtained by the investigator.

Table 12. Baseline conditions at Study Entry (ITT): Study 3001

	Glulisine (N=339) n (%)	Lispro (N=333) n (%)
Smokers	11 (3.2)	14 (4.2)
Hyperlipidemia/hypercholesterolemia	38 (11.2)	35 (10.5)
Peripheral arterial vascular disease/amputation	3 (0.9)	2 (0.6)
Microalbuminuria	4 (1.2)	4 (1.2)
CVA	4 (1.2)	1 (0.3)
Angina[⊥]	4 (1.2)	2 (0.6)
Past myocardial infarction	4 (1.2)	2 (0.6)
Past angioplasty/PCI	2 *--	2(0.6)
Past CABG**	4 --	4--
Coronary artery disease***	2 (0.6)	2 (0.6)
Hypertension	71 (20.9)	57 (17.1)
Subjects with ≥ 1 coronary condition	8 (2.4)	6 (1.8)
Subjects with ≥ 1 coronary condition or peripheral arterial disease or CVA	13 (3.8)	9 (2.7)

[⊥] One subject in each group included with history of atypical chest pain.
*Represents 1 subject with 2 past PCI.
**In both glulisine and lispro groups these actually represent 3 subjects with one subject (each group) having 2 prior CABG procedures.
***Reported terms include: ischemic heart disease and coronary artery disease.

Baseline (adjusted)[3] mean (SE) SBP was 124 (0.74) mm Hg for glulisine patients and 122 (0.75) mm Hg for lispro patients (adjusted mean difference (SE) was 2.2 (1.03) mm Hg with a 95% CI (0.1, 4.2), p=0.037). There were no significant changes from baseline at endpoint.
There were no significant differences between glulisine and lispro in baseline DBP or HR.[4]

Cardiovascular Safety Results:

Treatment-emergent adverse events are displayed in the next table. These AE were all reported after the start of study drug.

[3] For blood pressures and heart rate, an analysis of variance was used with treatment and pooled center as fixed effects. Source: sponsor, Study 3001, Table 12-140, p. 375, 377.
[4] Baseline (adjusted) mean (SE) DBP was 75.3 (0.48) mm Hg for glulisine patients and 74.5 (0.49) mm Hg for lispro patients (adjusted mean difference was 0.7 (0.67) mm Hg; p=NS). Baseline (adjusted) mean (SE) heart rate was 74.3 (0.54) bpm for glulisine and 73.1 (0.55) bpm for lispro (p=NS for the difference).

Table 13. Study 3001: Treatment-emergent AE by organ class: cardiac disorders (ITT)

System organ class Preferred term	Glulisine (N=339) N (%)	Lispro (N=333) N (%)
Cardiac disorders*	9 (2.7)	1 (0.3)
Acute myocardial infarction	2 (0.6)	--
Angina pectoris	2 (0.6)	--
Coronary artery disease NOS	2 (0.6)	--
Tachycardia NOS	2 (0.6)	--
Cardiovascular disorder NOS	1 (0.3)	--
Myocarditis NOS	1 (0.3)	--
Palpitations	1 (0.3)	--
Mitral valve prolapse	--	1 (0.3)

*p-value = 0.0206 from Fisher's exact test (for screening purposes only). The numbers (individual AE) are not additive (to the total Cardiac disorders) because a patient may have had more than one adverse event.

Serious AE: Five glulisine and no lispro patients experienced a serious cardiac AE (these are also listed under treatment-emergent AE). These five cases are summarized below.

Adverse events leading to withdrawal: Two glulisine and three lispro patients experienced an adverse event leading to withdrawal. Of the two glulisine cases, one patient suffered a myocardial infarction (see Narratives, below); the other case involved an eye disorder (retinopathy).

Deaths: None reported in this study.

Narrative and case report form review: serious cardiac AE: Study 3001:

1. Patient # 0806/06 (glulisine and glargine): 70 year old White male with type 1 DM and diabetic neuropathy started glargine on 9/20/2001 and study medication on 10/26/2001. Symptomatic hypoglycemia was noted in Sept. (6 episodes), Oct. (3), Nov. (2), Dec. (2), Jan. (1), Feb (3), March (2) and April (3). He reported atypical chest pain and effort dyspnea and underwent scan followed by cardiac catheterization ——— Coronary artery disease was found with the decision made for medical management. The adverse event was classified as serious because it required hospitalization. Study medication was continued without change and patient completed the study. Coded as: Coronary artery disease.

2. Patient # 0911/11 (glulisine and glargine): 46 year old White male with type 1 DM, hypertension, chronic atrial fibrillation, h/o "myocardial insufficiency" and "recidivation of pectanginal discomforts", started glargine on 12/12/2001 and study medication on 10/11/2001. On ——— he was noted to have "symptoms of coronary heart disease" (unspecified but requiring or prolonging hospitalization). He was treated with aspirin and hospitalized on ——— for invasive cardiac procedures which showed diffuse coronary artery disease, good left ventricular function, multiple cardiac risk factors (DM, hypertension, hyperlipidemia, smoking and family history) and chronic atrial fibrillation. He was treated with digitoxin, carvedilol, losartan, dyazide and atorvastatin, discharged, continued on study medication and continued on extension study 3011. Also noted in the CRF are multiple episodes of symptomatic hypoglycemia (8 in 9/2001, 6 in 10/2001, 5 in 11-12/2001, 7 in 1/2002, 7 in 2/2002, 6 in 3/2002, and 1 in 9/2002). Coded as: Coronary artery disease.

3. Patient # 1503/02 (glulisine and glargine): 27 year old White male with type 1 DM, retinopathy, started glargine on 11/5/2001 and study drug on 12/6/2001, presented with 2 episodes chest pain and ECG changes; myocarditis was suspected. On ——— the patient was hospitalized with ECG changes, tremor and post-infectious asthenia; he was discharged on ——— On 4/12/2002 it was

noted in the CRF that the ECG changes were present on a previous tracing and myocarditis was no longer suspected. On ——— he was again hospitalized with chest pain and ECG changes and discharged the next day. Coded as: myocarditis (2 events, coded on———————). The patient completed the study without change in study medication.

4. Patient #1401/05 (glulisine and glargine): 61 year old White female with type 1 DM, diabetic neuropathy, retinopathy (s/p photocoagulation), hypertension, started glargine on 12/11/2001 and study medication on 1/7/2002. The CRF records 9 episodes of symptomatic hypoglycemia during 12/2001 as well as 9 episodes of symptomatic hypoglycemia during January through February, 2002. On ——— she developed chest pain, palpitations and hypertension (there is no record of heart rate of blood pressure). Because of suspected angina, the patient was hospitalized and was discharged on ——— with a diagnosis of angina pectoris. Study medications were continued without change. On ——— , the patient developed acute pain and dyspnea and was hospitalized with a myocardial infarction. On ——— she underwent cardiac catheterization followed by stent placement and discharge on ——— Coded as: angina pectoris (event 1, ——— · study medication discontinued and reintroduced), acute myocardial infarction (event 2, ——— · study medication discontinued and patient withdrawn from study).

5. Patient # 1202/09 (glulisine and glargine): 52 year old White male with past history of myocardial infarction (1991), rare ("seldem") angina, hypertension, hyperlipidemia, began glargine on 12/3/2001 and study medication 1/6/2002, developed chest pain and was admitted ——— with an anteroseptal myocardial infarction. Coded as: acute myocardial infarction (——— ; no change in study medication). According to the CRF, study medications were unchanged and the patient underwent PTCA (———). On 2/10/2002, Angina pectoris was noted as an AE (did not meet seriousness criteria) and study medications were unchanged. The patient completed the study.

Other cardiac (non-serious) AE from Study 3001: case report form review:

1. Patient #0701/07 (glulisine and glargine) 38 year old White male with type 1 DM, retinopathy, mild asthma, migraine, no h/o hypertension (baseline BP was 145/90), started glulisine 11/28/2001. Symptomatic hypoglycemia episodes were noted in November, 2001 (14 episodes), December, 2001 (5), January-February, 2002 (8), April-May (5) and June (2). An SAE report of severe hypoglycemia was noted 1/3/2002. Palpitation, beginning in——————— and ending in——————— was recorded as an AE; study medication was unchanged and no remedial medication was given. No pulse or ECG result was recorded in the CRF.
2. Patient #0801/08 (glulisine and glargine) 25 year old White female with type 1 DM, hypercholesterolemia, started study drug 11/24/2001. Tachycardia is reported as a non-serious AE in 11/2001 (unclear as to exact day); no associated pulse, glucose or ECG result was recorded in the CRF. Study medication was unchanged and no remedial medication was given. Five episodes of symptomatic hypoglycemia were recorded in 11/2001 (with a total of 18 episodes in the CRF).
3. Patient #0803/03 (glulisine and glargine): 29 year old White female with type 1 DM, retinopathy, neuropathy, and hypertension, started study drug 10/24/2001. Tachycardia is reported as a non-serious AE on 1/4/2002; no associated pulse, glucose or ECG result was recorded in the CRF. Study medication was unchanged and no remedial medication was given. Tachycardia (no pulse given) was noted on the ——— physical examination (not mentioned in the baseline examination).
4. Patient #0911/20 (glulisine and glargine): 44 year old White female with type 1 DM, retinopathy (s/p photocoagulation), neuropathy, started study drug 11/21/2001. On ———the non-serious AE "circulatory disorder," deemed mild in intensity was recorded; symptoms and diagnosis are not given. Study medications were not changed and remedial medication was not given. About 80 listings of "symptomatic hypoglycemia" are also recorded (some glucoses listed are > 70 mg/dl).

QT analyses:

Preclinical findings:
In a cardiovascular pharmacology study (F2001PHM0012), 3 conscious beagles were administered glulisine at doses of 0.3 or 1.0 UI/kg sc. Glucoses were apparently not measured in this study although glucose levels decreased in other studies with similar dose regimens; however, glulisine administration was associated with a slight decrease in SBP, increased HR, and increased QTcB (42 ms after the 0.3 IU/kg dose and 52 ms after the 1.0 IU/kg dose) and QTcF (19 ms after the 0.3 IU/kg dose and 27 ms after the 1.0 IU/kg dose). According to the sponsor, QT prolongation due to hypoglycemia has been documented in both preclinical and human models. ECGs were also evaluated in 1-month and 6-month toxicity studies where glulisine 1.0 IU/kg was administered to dogs. ECGs were performed when the dogs were euglycemic and showed no changes in PR, QRS, QT or HR.

This reviewer was unable to find other components of a QT evaluation (including *in vitro* testing).

Study 1016: ECG analyses:
In this study, a blinded ECG review was performed in 16 nondiabetic men , 18-45 years, with particular emphasis on repolarization. This was a single-center, randomized, open-label, 2-way crossover study. Glulisine and regular insulin were administered by intravenous infusion for a 120 minute period in a crossover manner; subjects were maintained euglycemic by concurrent intravenous glucose infusion using the euglycemic clamp technique. ECGs were recorded at screening, immediately prior to infusion, 90 minutes after starting infusion (when insulin levels had reached steady state of approximately 70 µIU/ml, at end of clamp (360 minutes after starting clamp) and at follow-up (8 measurements per subject). ECGs were over-read by a blinded expert reviewer.

Table 14: ECG conduction parameters: mean (SD) at 0 minutes and change to 90 and 360 minutes: healthy young men (Study 1016)

	Mean (SD) or mean change (SD) (ms)					
	Glulisine (N=16)			Regular insulin (N=16)		
Conduction parameter	0 min.	Change to 90 min.	Change to 360 min.	0 min.	Change to 90 min.	Change to 360 min.
PR	161.9 (23.03)	-1.6 (9.24)	-12.1 (10.16)	157.5 (25.73)	6.0 (14.39)	-8.3 (14.66)
QRS	96.8 (9.98)	1.9 (5.49)	-0.5 (5.19)	97.1 (9.55)	3.6 (5.94)	-0.8 (5.21)
QT	423.1 (31.98)	-9.0 (25.65)	-27.8 (19.50)	419.4 (32.62)	-3.5 (23.69)	-21.3 (17.09)
QTcB	403.4 (19.85)	2.6 (19.64)	4.6 (16.49)	406.6 (18.83)	0.0 (13.65)	-2.8 (11.15)

In reviewing mean differences in QtcB between treatment groups (Table S-78), there were no significant differences between the two groups.

ISSUES & COMMENTS:

1. **Cardiac events:** As the sponsor acknowledges, there is an imbalance in cardiac events in the group with type 1 DM (not seen in the patients with type 2 DM). These events appear to be driven by study 3001. A review of the individual events (from the case report forms and narratives) yields insufficient information to conclude that these cardiac events are an effect of the glulisine treatment; this reviewer, however, cannot determine from the available information whether or not the cardiac TEAE or serious AE were related to hypoglycemia. A review of baseline characteristics reveals an imbalance in hypertensives (more on glulisine) and baseline SBP (significantly higher in the glulisine

group) compared to the comparator; this imbalance confounds the safety results (as coronary disease is more likely in patients with multiple risk factors). Other baseline imbalances include: longer time from diabetes diagnosis and higher incidence of retinopathy and neuropathy. If one were even postulating an increase in myocardial infarction or angina in glulisine-treated patients, then the reported events are too few in number to draw conclusions. In addition, if glulisine caused an increase in myocardial infarction (for example) one would have also expected an increase in congestive heart failure and death (not seen in this submission). This review cannot rule out cardiac effects (for example, tachycardia, or angina, or myocardial infarction) due to hypoglycemia. The sponsor, in the submission, claims that there was no relationship with hypoglycemia and cardiac events; however there was insufficient documentation in the case report form for this reviewer to arrive at similar conclusions. Finally, the small database of long-term exposure in patients with type 1 DM is inadequate to answer the question of cardiovascular risk.

2. **QT effects**: To summarize, QT increases and HR/BP effects were seen in one glulisine beagle study where glucoses (judging from the study report) apparently were not measured . Two other (one and six-month) animal studies were apparently negative. An active controlled study of glulisine (vs. insulin) administered to healthy men, where euglycemia was maintained, did not reveal a safety signal; however, this study used a small sample size and did not employ a positive control. The sponsor did not include other QT evaluations.

   In the literature, QT prolongation is described in association with hypoglycemia (see references (ref). 1, 5), hyperglycemia (refs. 5, 6) and, from epidemiologic data, in subjects with diabetes (refs. 3, 4).

   Given the inadequate QT workup, and subsequent limitations of the available information (no glucose levels measured in the beagle study with QT increases; lack of *in vitro* data; small sample size and no positive control in the human study), this reviewer is unable to make definitive interpretations. If your Division would like a more definitive exploration of QT effects, then you might consider asking the sponsor to perform a "thorough QT study" using an active control (such a regular insulin), positive control (such as moxifloxacin) and maintain euglycemia so that hypoglycemic/hyperglycemic states will not confound the outcome. The sample size should take into account the baseline variance in this current study.

Recommendations:

1. As above, if your Division wishes to fully explore the QT issue, then we would recommend a "thorough" QT study, with an adequate sample size, using an active (insulin) and positive control (moxifloxacin), maintaining euglycemia, and exploring an adequate range of dosing.
2. Your Division should consider asking for more long-term safety data in patients with type 1 DM.

Should you have any further questions please feel free to contact me or the Divsion.

References:

1. Robinson RT et. al. Mechanisms of abnormal cardiac repolarization during insulin-induced hypoglycemia. Diabetes 2003 Jun; 52 (6): 1469-74.
2. Gastaldelli A et. al. Insulin prolongs the QTc interval in humans. Am J Physiol Regul Integr Comp Physiol. 2000 Dec; 279 (6): R2022-5.
3. Brown DW et. al. Impaired fasting glucose, diabetes mellitus, and cardiovascular risk factors are associated with prolonged QTc duration. Results from the Third National Health and Nutrition Examination Survey. J Cardiovasc Risk. 2001 Aug; 8 (4): 227-33.
4. Fauchier L et. al. Association between heart rate-corrected QT interval and coronary risk factors in 2,894 healthy subjects (the DESIR study). Data from an Epidemiological Study on the Insulin Resistance syndrome. Am J. Cardiol. 2000 Sep 1; 86 (5): 557-9, A9.
5. Zhang Y et. al. Impairment of human ether-a-go-go-related gene (HERG) K+ channel function by hypoglycemia and hyperglycemia. Similar phenotypes but different mechanisms. J Biol Chem. 2003 Mar 21; 278 (12) 10417-26. Epub 2003 Jan 16.

6. Marfella R et. al. The effect of acute hyperglycemia on QTc duration in healthy man. Diabetologia. 2000 May; 43 (5): 571-5.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Shari Targum
12/23/03 02:51:26 PM
MEDICAL OFFICER

Norman Stockbridge
12/23/03 03:24:00 PM
MEDICAL OFFICER
For Douglas Throckmorton

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC - 8 2003

Dear Dr. . ——

Between October 14 and 22, 2003, Mr. Joel Martinez, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol #HMR1964A/3002 entitled: "26-Week, Multinational, Multicenter, Controlled, Open, 1:1 Randomized, Parallel Clinical Trial Comparing HMR1964 with Regular Insulin Injected Subcutaneously in Subjects with Type 2 Diabetes Mellitus Also Using NPH Insulin, and Which Will Lead into a Comparative 26-Week Safety Extension Study (HMR1964A/3012))" of the investigational drug Apidra™ (insulin glulisine [rDNA origin]), performed for Aventis Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your October 22, 2003 written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Martinez presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not adhere to the investigational plan [21 CFR 312.60].

   a. The protocol specified that subjects not require continuous insulin therapy since diagnosis. Subjects 0024, 0029, and 0030 had received continuous insulin therapy since diagnosis with Type 2 diabetes mellitus, yet these subjects were enrolled in the study.

   b. The protocol required that subjects with impaired renal function, as shown by, but not limited to serum creatinine > 2.0mg/dL at visit 1 be excluded from the study. Subject 0042 had a serum creatinine level of 2.4mg/dL at visit 1, yet was enrolled in the study.

   c. The protocol required twice daily dosing with NPH insulin. Subject 0010 administered NPH insulin once a day through visit 14, and subject 0029 administered NPH insulin once a day up to one day prior to visit 11.

2. You did not promptly report to the IRB all unanticipated problems involving risk to human subjects [21 CFR 312.66] in that a total of 11 serious adverse events (SAEs) occurring between 10/11/01 and 3/20/02 for subjects 0004, 0015, 0025, 0034, and 0039, were not initially reported to the IRB until October 13, 2003.

3. You did not maintain adequate records of the disposition of the drug [21 CFR 312.62(a)] in that you did not maintain documentation to assure that the re-labeling procedure on 22 vials of HMR 196 was carried out as specified in the labeling instruction sheet.

4. You did not maintain adequate and accurate case histories [21 CFR 312.62(b)] in that for subject 0001, a source document reports that the subject started treatment with insulin in July 1997; however the case report form (CRF) reports an insulin start date of --/--/1999.

We trust that the corrective actions outlined in your October 22, 2003 written response, will assure that the findings noted above are not repeated in an ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Martinez during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

/S/

Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

CFN/FEI: 100051692
Field Classification: VAI
Headquarters Classification:
_____1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_X__4)VAI-RR, response received and accepted
_____5)OAI

Deficiencies noted:
_X___inadequate drug accountability (04)
_X___failure to adhere to protocol (05)
_X___inadequate and inaccurate records (06)
_X___failure to notify IRB of changes, failure to submit progress reports (15)

Deficiency Codes: 4, 5, 6, 15
cc:
HFA-224
HFD-510 Doc.Rm. NDA#21-629
HFD-510 Review Div.Dir/Orloff
HFD-510 MO/Zawadzki
HFD-510 PM/Rhee
HFD-46/47c/r/s/ GCP File #7053
HFD-46/47 GCP Reviewer/Slavin
HFR-SW150 DIB/Thornburg
HFR-SW1540 Bimo Monitor/Martinez
HFR-SW1540 Field Investigator/same as BIMO Monitor
GCF-1 Seth Ray

r/d: (AS): 12/2/03
reviewed:KMU:12/5/03
f/t:sg:12/8/03

[redacted]

Reviewer Note to Rev. Div. M.O.
This was a routine inspection initiated pursuant to the approval of Apidra™ (insulin glulisine). This site screened 49 subjects and randomized 40 subjects. Thirty-six subjects completed the study. All subjects' records were reviewed for adverse events and for informed consent. Twenty subjects' records were audited for data integrity. Note: the primary endpoint could not be verified because the site only had access to the screening (visit 1) GHb results, the site was blinded to GHb results at visits 6, 13, and 15. At the completion of the inspection, a 6-item Form FDA 483 was issued to Dr. [redacted] All of the items have been cited in the letter. In addition, it was noted, and discussed with Dr. [redacted] that for several subjects, the pre-prandial

and post-prandial blood glucose values were not within the target ranges specified in the protocol, (90-120 mg/dL)—pre-prandial, and (120-160mg/dL)—post-prandial.
Dr [redacted] explained that they tried to meet these target ranges, and that subjects were provided with educational materials to assist them in titrating their insulin dosages. Dr. [redacted] also stated that insulin absorption is very variable, and that glucose meters have up to a 15% error rate.

Dr. [redacted] has submitted an acceptable response to the Form FDA 483. The inspection is classified as VAI-RR (response received and accepted). Data are acceptable in support of NDA 21-629.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Khin U
12/10/03 11:14:03 AM

3 **page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.**

(b4)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: November 25, 2003

To: Odile Ernoux, M.D.	**From:** Julie Rhee
Company: Aventis Pharmaceuticals Inc.	Division of Division of Metabolic and Endocrine Drug Products
Fax number: (908) 304-6318	**Fax number:** (301) 443-9282
Phone number: (908) 231-3536	**Phone number:** (301) 827-6424

Subject: NDA 21-629 Apidra (insulin glulisine [rDNA origin])

Total no. of pages including cover: 2

Comments:

Additional statistical information request. Please let me know when we could expect your reasponse. Thank you.

Document to be mailed: ☐ YES ☑ NO

NDA 21-629 Apidra (insulin glulisine [rDNA origin])

Date of submission: June 18, 2003

Additional information request from Biometrics

Please provide 3 datasets (one each) for Studies 3001, 3002, and 3004.

The datasets you provide should be similar to efficacy datasets already provided and have only two outcome variables, HbA1c and insulin dose. For insulin dose, please provide data for the amount of insulin at baseline and insulin dose change from baseline for each visit and at endpoint. The datasets should also include randomization stratum and pooled center if not already included in previously submitted datasets.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Julie Rhee
11/25/03 03:25:29 PM

November 24, 2003

Dr. David Orloff
Director, Division of Metabolic and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

NDA 21-629: APIDRA™
HMR 1964 – Insulin glulisine (rDNA human insulin analog)
Response to November 12, 2003 request

Dear Dr. Orloff:

Reference is made to the above-mentioned New Drug Application (NDA) for APIDRA™ (HMR 1964 – insulin glulisine), which was submitted to the Agency on June 18, 2003.

The purpose of this November 24, 2003 correspondence is to submit a table summarizing baseline cardiovascular conditions for the HMR1964A3001 study in response to your November 12, 2003 request.

In preparing the requested table for a summary of specific (cardiac related) baseline conditions in the 'intention-to-treat' patient population in HMR1964A3001 a blinded review of all unique verbatim terms provided by the investigator specifically on the "relevant past medical history", CRF Pages 8 & 9, and "relevant past surgical history", CRF Page 10, from this study was conduced by the Global Coding team.

Verbatim terms were labeled with a diagnosis and then grouped together into higher level groupings (HLG) e.g. Verbatim 'high cholesterol' was labeled Hypercholesterolemia and grouped together with Hyperlipidemia, Hypertriglyceridemia, etc into the HLG of Hypercholesterolemia/hyperlipidemia. The HLGs correspond to the conditions requested for production of the table. Verbatim terms with more than one medical concept were labeled to capture each concept separately e.g. "Angina post CABG" was labeled with both "Angina pectoris" and "CABG". Investigator reported verbatim terms that described only additional detail to the chosen body system were labeled using the body system as the diagnosis e.g. 'since 2000' reported on the CRF next to Hypertension was labeled Hypertension.

The unique term list with the labels and groupings were over-read in a blinded as to treatment fashion by an Aventis physician. The unique terms were then matched programmatically with the subject data in SAS for the creation of the analysis table and subject listings.

The requested table is provided, supplemented by baseline cardiovascular conditions i.e. 'Coronary artery disease' and 'Hypertension', that may be of interest to the medical reviewer and were not captured under the specific terms requested.

To assist the medical reviewer in understanding the terms from which the table was constructed, two listings have been attached. Listing 1 entitled "Baseline conditions at study entry (ITT) in

Study 3001" included in Table 1 provides the baseline cardiovascular conditions from subjects who were included in the table. Listing 2 entitled "All other baseline conditions at study entry (ITT) in Study 3001 not used in table 1" provides all other verbatim terms in the "relevant past medical history" and "relevant past surgical history" CRF modules that were not included in Listing 1.

This submission is fully electronic and provided on the enclosed CD (approximately 1MB). The submission consists of the above-mentioned Table 1, Listing 1 and Listing 2, which are located in the *N21629 / clinstat / other* folder. Aventis certifies that all electronic media have been scanned and found to be free of any known computer viruses (Norton AntiVirus Corporate Edition; program 7.50.846, Scan Engine 4.1.0.6, Version 51119s, November 19, 2003). In addition, an original signed Cover Letter and Form FDA 356h are provided in paper form.

Aventis Pharmaceuticals Inc. looks forward to working with the Division to facilitate the review of the APIDRA™ NDA. Should you have any questions regarding this material, please contact the undersigned by telephone at (908) 231-3536 or by fax at (908) 304-6318 or, in my absence, please contact Steve Caffé, M.D. by telephone at (908) 231-5863.

Sincerely,

Chanda Mosely for Odile Emoux

Odile Emoux, M.D.
Director, Regulatory Affairs
Aventis Pharmaceuticals, Inc.
Phone: (908)-231-3536
Fax: (908)-304-6318

November 20, 2003

Dr. David Orloff
Director, Division of Metabolic and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

NDA 21-629: APIDRA™
HMR 1964 – Insulin glulisine (rDNA human insulin analog)
Response to October 17, 2003 request (item 2): CRF submission

Dear Dr. Orloff:

Reference is made to the above-mentioned New Drug Application (NDA) for APIDRA™ (HMR 1964 – insulin glulisine), which was submitted to the Agency on June 18, 2003.

The purpose of this November 20, 2003 correspondence is to submit CRFs in response to your October 17, 2003 *Request # 2*. Specifically requested were patient profiles and CRFs for all patients with cardiac TEAEs in the different studies. The requested patient profiles were submitted to the Agency on November 14, 2003. Information regarding *Request # 1 and # 3* of your October 17, 2003 correspondence were submitted on November 11, 2003.

This submission is fully electronic and provided on the enclosed DLT (approximately 1 GB). Aventis certifies that all electronic media have been scanned and found to be free of any known computer viruses (Norton AntiVirus Corporate Edition; program 7.50.846, Scan Engine 4.1.0.6, Version 51117v, November 17, 2003). In addition, an original signed Cover Letter and Form FDA 356h are provided in paper form.

This submission consists of CRFs that are located in the *crf* folder. Within this folder, the following study subfolders are given: 3001, 3002, 3004, 3005, 3006, 3011, and 3012. The CRFs are organized by site within the above-mentioned study subfolders. Please note that the submitted CRFs are not bookmarked. Once they become available, however, the bookmarks can be provided to the Agency upon request.

Aventis Pharmaceuticals Inc. looks forward to working with the Division to facilitate the review of the APIDRA™ NDA. Should you have any questions regarding this material, please contact the undersigned by telephone at (908) 231-3536 or by fax at (908) 304-6318 or, in my absence, please contact Steve Caffé, M.D. by telephone at (908) 231-5863.

Sincerely,

Chanda Morseth for Odile Ernoux

Odile Ernoux, M.D.
Director, Regulatory Affairs
Aventis Pharmaceuticals, Inc.
Phone: (908)-231-3536
Fax: (908)-304-6318

November 14, 2003

Dr. David Orloff
Director, Division of Metabolic and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

NDA 21-629: APIDRA™
HMR 1964 – Insulin glulisine (rDNA human insulin analog)
Response to October 17, 2003 request (item 2)

Dear Dr. Orloff:

Reference is made to the above-mentioned New Drug Application (NDA) for APIDRA™ (HMR 1964 – insulin glulisine), which was submitted to the Agency on June 18, 2003.

The purpose of this November 14, 2003 correspondence is to submit patient profile information in response to your October 17, 2003 *Request # 2*. Specifically requested were patient profiles and CRFs for all patients with cardiac TEAEs in the different studies. The requested CRFs will be submitted by November 21, 2003. Information regarding *Request # 1 and # 3* of your October 17, 2003 correspondence were submitted to the Agency on November 11, 2003.

This submission is fully electronic and provided on the enclosed CD (approximately 15 MB). Aventis certifies that all electronic media have been scanned and found to be free of any known computer viruses (Norton AntiVirus Corporate Edition; program 7.50.846, Scan Engine 4.1.0.6, Version 51112s, November 12, 2003). In addition, an original signed Cover Letter and Form FDA 356h are provided in paper form.

This submission consists of patient profile information that is located in the *N21629 / crt / profile* subfolder. Within this subfolder, patient profiles are organized by study as follows: 30013011 (studies 3001 and 3011 combined), 30023012 (studies 3002 and 3012 combined), 3004, 3005, and 3006.

Aventis Pharmaceuticals Inc. looks forward to working with the Division to facilitate the review of the APIDRA™ NDA. Should you have any questions regarding this material, please contact the undersigned by telephone at (908) 231-3536 or by fax at (908) 304-6318 or, in my absence, please contact Steve Caffé, M.D. by telephone at (908) 231-5863.

Sincerely,

Odile Ernoux, M.D.
Director, Regulatory Affairs
Aventis Pharmaceuticals, Inc.
Phone: (908)-231-3536
Fax: (908)-304-6318

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: November 12, 2003

To: Odile Ernoux, M.D.	**From:** Julie Rhee
Company: Aventis Pharmaceuticals Inc.	Division of Division of Metabolic and Endocrine Drug Products
Fax number: (908) 304-6318	**Fax number:** (301) 443-9282
Phone number: (908) 231-3536	**Phone number:** (301) 827-6424

Subject: NDA 21-629 Apidra

Total no. of pages including cover: 2

Comments:

Please provide additional cardiaovascular information requested on the attached page. Please let me know when we could expect your response. Thank you.

Document to be mailed: ☐ YES ☑ NO

Table 1. Baseline conditions at study entry (ITT) in Study 3001

Number of patients and (%)	Glulisine (N=339)	Lispro (N=333)
Smokers		
Hyperlipidemia/hypercholesterolemia		
Peripheral vascular disease		
Microalbuminuria		
Transient ischemic attacks		
Angina		
Past myocardial infarction		
Past angioplasty/PCI		
Past CABG		

Please indicate separately in text if any of the patients have had more than one of the cardiac events.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Julie Rhee
11/12/03 11:45:53 AM

November 11, 2003

Dr. David Orloff
Director, Division of Metabolic and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

NDA 21-629: APIDRA™
HMR 1964 – Insulin glulisine (rDNA human insulin analog)
Response to October 17, 2003 request (items 1 and 3)

Dear Dr. Orloff:

Reference is made to the above-mentioned New Drug Application (NDA) for APIDRA™ (HMR 1964 – insulin glulisine), which was submitted to the Agency on June 18, 2003.

We are submitting the information related to requests 1 and 3 of your mail dated October 17, 2003. Information pertaining to request 2 (patient profiles and CRFs) will be submitted by November the 14th for the profiles and by November 21st for the CRFs.

You can find bellow a detailed description of the information and data that is presented in the attached tables.

Request 1:

Data was requested for all subjects with treatment emergent cardiac adverse events by study for study 3001, 3002, 3004, 3005, 3006, 3011 and 3012. Studies 3011 and 3012 are the six months extensions to studies 3001 and 3002, respectively. In these extensions all subjects continued on the study medication to which they were allocated during the initial 26-week study. For purposes of presentation, the 52-week analysis of studies 3001/3011 and 3002/3012 is presented which contains all TEAEs reported in either study. The 52-week analysis treatment phase is defined as the period from the date of the first dose of study medication in study 3001 or 3002 to the date of the last dose of study medication whether it is in the initial 26-week study or in the 26-week extension study. Thus, the population used in this analysis includes subjects who may have been treated only in the initial 26-week study.

The data used for the requested columns is as follows.

- " History of cardiovascular disease" is defined based on entries extracted from the relevant diseases/illnesses in the subject's medical history CRF under the listing "Cardiovascular disease" as completed by the investigator. The investigator was given two lines to record any history of cardiovascular disease under this heading. If a subject had at least one entry under this heading then the subject was classified as having a "history of cardiovascular disease". The date of the patient's age at the time of the relevant cardiac disease was not collected and therefore is not presented.

- The smoking status of the subject was not collected and therefore is not presented.
- Under the column of "cardiac evaluation during the study", the reviewer is provided a link to the subject narrative which provides information provided to the sponsor on evaluations done during the study. These narratives were based on CIOMS reports by the sites to the Aventis Pharmacovigilance department. Since CIOMS reports are only collected on subjects reporting serious adverse events, narratives are not available for subjects reporting non-serious cardiac TEAEs.
- The time interval between "first study medication" and the first severe/serious hypoglycemic episode is provided under the column "time to onset of hypoglycemia". If a subject did not have a severe/serious hypoglycemic episode, no time is given.
- No specific CRF collected an assessment by the investigator indicating if a TEAE was related to a hypoglycemic episode. A search of the database was made to determine if a severe/serious hypoglycemic episode occurred on the same calendar day as the start date for the cardiac TEAE. If a severe/serious hypoglycemic episode occurred on the same calendar day as the first day of the cardiac TEAE then a "yes" response was provided in this column for the TEAE being related to hypoglycemia.
- The investigator's response to the question on the AE CRF as to whether the AE was possibly related to study medication was extracted to assess if the TEAE was related to study medication.

Request 3:

By study tables are presented summarizing the cardiac history of subjects at the time of screening into the study. Data was requested by study for study 3001, 3002, 3004, 3005, 3006, 3011 and 3012. As for request 1, for purposes of presentation, the 52-week analysis of studies 3001/3011 and 3002/3012 is presented.

A working definition of "cardiac disease" at the time of screening was made based on entries extracted from the "Relevant diseases/illnesses" CRF under the listing "Cardiovascular disease" as completed by the investigator. The investigator was given two lines to record any history of cardiovascular disease under this heading. If a subject had at least one entry under this heading then the subject was classified as having "cardiac disease". The same definition was used to classify a subject as having a "history of cardiac disease" for request 1.

A subject was classified as having hypertension if any of the following parameters were present: systolic blood pressure >140 mmHg at baseline, diastolic blood pressure >90 mmHg at baseline, use of a concomitant medication prior to randomization or the investigator indicated a positive response in the "Relevant diseases/illnesses" CRF under the listing "Hypertension".

A subject was classified as having hyperlipidemia due to an elevation in LDL exceeding 130 mg/dl or use of a concomitant lipid lowering medication.

A subject was classified as having hyperlipidemia due to an elevation in triglycerides exceeding 180 mg/dl or use of a concomitant lipid lowering medication.

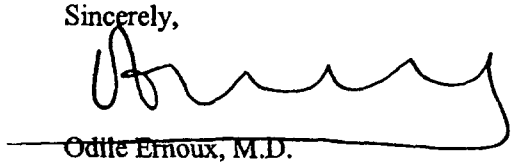
The smoking status of the subject was not collected and therefore is not presented.

This submission is fully electronic and provided on the enclosed CD (approximately 10 MB). Aventis certifies that all electronic media have been scanned and found to be free of any known computer viruses (Norton AntiVirus Corporate Edition; program 7.50.846, Scan Engine 4.1.0.6, Version 51024u, November 5, 2003). In addition, an original signed Cover Letter and Form FDA 356h are provided in paper form.

This submission consists of files that can be located in the -N21629/clinstat/other- subfolder. "sum_history_cardiac.pdf" contains the responses to your requests 1 and 3 organized by study. As per your request, it is also provided as a MS Word document. You can also access this MS Word version by clicking on the icon located at the top of every page of "sum_history_cardiac_pdf" file. The other files contain the narratives for each individual study and 2 appendices for ATC codes.

Aventis Pharmaceuticals Inc. looks forward to working with the Division to facilitate the review of the APIDRA™ NDA. Should you have any questions regarding this material, please contact me at 908-231-3536 or by fax at 908-304-6318 or, in my absence, please contact Steve Caffé, M.D. by telephone at 908-231-5863.

Sincerely,



Odile Emoux, M.D.
Director, Regulatory Affairs
Aventis Pharmaceuticals, Inc.
Phone: (908)-231-3536
Fax: (908)-304-6318

Rhee, H Julie

From: Rhee, H Julie
Sent: Monday, November 10, 2003 3:36 PM
To: Orloff, David G
Cc: Zawadzki, Joanna K
Subject: FW: glulisine

David,

I am forwarding this e-mail to get your concurrence before I fax the document to the sponsor.

Joanna added one sentence after the table.

Thanks,

Julie

11_10_03
dio info request.

Table 1. Baseline conditions at study entry (ITT) in Study 3001

Number of patients and (%)	Glulisine (N=339)	Lispro (N=333)
Smokers		
Hyperlipidemia/hypercholesterolemia		
Peripheral vascular disease		
Microalbuminuria		
Transient ischemic attacks		
Angina		
Past myocardial infarction		
Past angioplasty/PCI		
Past CABG		

Please indicate separately in text if any of the patients have had more than one of the cardiac events.

-----Original Message-----
From: Zawadzki, Joanna K
Sent: Monday, November 10, 2003 10:02 AM
To: Rhee, H Julie; Targum, Shari
Cc: Zawadzki, Joanna K
Subject: FW: glulisine

Shari,

I am forwarding this request to our project manager to forward to the sponsor. We have previously requested additional cardiac data, which we have not yet received. Some of the previous request overlaps with your table, which should facilitate the sponsor's completing this table.

Thanks,

Joanna

-----Original Message-----
From: Targum, Shari
Sent: Thursday, November 06, 2003 11:59 AM
To: Zawadzki, Joanna K
Subject: glulisine

Joanna,
I've been going through the glulisine data. One confounding factor in Study 3001 is the apparent baseline differences between the two groups (e.g., baseline hypertension (Table 21-30) 21% in glulisine group vs. 17% in lispro; and cardiovascular disease 4% in glulisine vs. 3% in lispro (small numerical difference here)). To "flesh out" the question of baseline imbalances (including risk factors for coronary disease), can the sponsor fill out a Table such as what I've

Table 1.
diac risk factors
inserted here? Thank you.

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Julie Rhee
11/12/03 11:40:21 AM
CSO

November 4, 2003

Dr. David Orloff
Director, Division of Metabolic and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

NDA 21-629: APIDRA™
HMR 1964 – Insulin glulisine (rDNA human insulin analog)
120Day Safety Update

Dear Dr. Orloff:

Reference is made to the above-mentioned New Drug Application (NDA) for APIDRA™ (HMR 1964 – insulin glulisine), which was submitted to the Agency on June 18, 2003. Reference is also made to the pre-NDA meeting held on November 25, 2002.

In conformance with 21 CFR 314.50(d)(5)(vi)(b), Aventis Pharmaceuticals Inc. is submitting the 120-day safety update for the APIDRA™ NDA. Included in this safety update are final data for the following Phase III studies not previously reported in the original NDA:

- **Studies 3011 and 3012: the 26-week extensions of Studies 3001 and 3002, respectively.** All subjects who successfully completed the initial 26-week study (3001 or 3002) and agreed to continue their study participation were to be enrolled into the respective extension study (3011 or 3012). Throughout the extension studies, subjects were to receive the same insulin preparations received in the initial 26-week study. Final clinical study reports for both extension studies are included in this submission.
- **Study 3005: a 26-week multinational, multicenter, randomized, open, parallel study in subjects with type 2 diabetes.** The overall design of Study 3005 was very similar to that of Study 3002. The two studies, however, were conducted in different geographical regions. Although the study report for Study 3005 is currently in preparation, all data and results from the study are included in the safety update.

Aventis Pharmaceuticals Inc. • 200 Crossing Boulevard • PO Box 6890 • Bridgewater, NJ 08807-0890 • www.aventis.com
Telephone (908) 304-7000

In this 120-day safety update, safety analyses have been updated to incorporate data from Studies 3005, 3011 and 3012. These analyses, which are included in the Summary of Clinical Safety update, are generally presented as follows:

- Studies in type 1 diabetes (3 studies): Studies 3001/3011, 3004, and 3006 pooled;
- Studies in type 2 diabetes (2 studies): Studies 3002/3012 and 3005 pooled;
- Pooled across all Phase III studies (5 studies): Studies 3001/3011, 3002/3012, 3004, 3005, and 3006 pooled.

The current findings on the safety of insulin glulisine are consistent with those presented in the original APIDRA™ NDA. Findings presented in this safety update further strengthen the conclusion that glulisine displays a safety profile similar to that of other short-acting insulin preparations. It has been shown that, in this clinical program in which 436 subjects received glulisine treatment for at least 52 weeks, the safety profile of glulisine is maintained over a 1-year exposure to the drug.

This submission is fully electronic, with the safety update provided electronically on the enclosed DLT 35/70 Digital Tape (3.3 GB). Aventis certifies that all electronic media have been scanned and found to be free of any known computer viruses (Norton AntiVirus Corporate Edition; program 7.50.846, Scan Engine 4.1.0.6, Version 51024u, October 24, 2003). In addition, an original signed Cover Letter and Form FDA 356h are provided in paper form.

The safety update submission consists of the following items, as indicated on the Form FDA 356h:

Items as described in Form FDA 356h and their location within the submission		
Item	**Description**	**Folder name**
8	clinical data section	clinstat
9	safety update report	update
11	case report tabulations	crt
12	case report forms	crf

Item 8, clinical data section (clinstat subfolder): Final clinical study reports, as well as appendices, for extension studies 3011 and 3012 are included in the safety update. Since the study report for Study 3005 is in preparation, an interim safety update for this study has been included in the safety update.

Item 9, safety update report (update subfolder): The safety update table of contents, which follows that of the Summary of Clinical Safety, and the safety update itself are contained within this subfolder.

Item 11, case report tabulations (crt subfolder): This subfolder contains SAS transport files (Xpt files) for Studies 3005, 3011 and 3012.

Item 12, case report forms (crf subfolder): Case report forms for Studies 3005, 3011 and 3012 are included in the crf subfolder.

Aventis Pharmaceuticals Inc. looks forward to working with the Division to facilitate the review of the APIDRA™ NDA. Should you have any questions regarding this material, please contact the undersigned by telephone at (908) 231-3536 or by fax at (908) 304-6318 or, in my absence, please contact Steve Caffé, M.D. by telephone at (908) 231-5863.

Sincerely,

Odile Ernoux, M.D.
Director, Regulatory Affairs
Aventis Pharmaceuticals, Inc.
Phone: (908)-231-3536
Fax: (908)-304-6318

October 24, 2003

Dr. David Orloff
Director, Division of Metabolic and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

NDA 21-629: APIDRA™
HMR 1964 – Insulin glulisine (rDNA human insulin analog)
Amendment to original NDA

Dear Dr. Orloff:

Reference is made to the above-mentioned New Drug Application (NDA) for APIDRA™ (HMR 1964 – insulin glulisine), which was submitted to the Agency on June 18, 2003.

During preparation of the study report for extension study 3011, it was discovered that, in the Study 3001 ClinTrial Database, 186 known units for the 7-point-self-measured blood glucose values were identified as missing due to an error in a Data Management process. The missing blood glucose values were from 27 subjects. These values have now been included in the database, and new analyses have been performed to include the initially omitted blood glucose values. The original clinical study report has been amended only for the purpose of incorporating these new analyses; no other changes have been made. The incorporated changes do not affect the overall conclusion from blood glucose analyses that were reported in the original 3001 study report.

In this October 24, 2003 correspondence, we submit the updated 3001 clinical study report as an amendment to the original NDA for APIDRA™. The updated report has been provided electronically on the enclosed CD ROM (approximately 250 megabytes) for your review. In addition, an original signed Cover Letter and Form FDA 356h are provided in paper form. Aventis certifies that all electronic media have been scanned and found to be free of any known computer viruses (Norton AntiVirus Corporate Edition; program 7.50.846, Scan Engine 4.1.0.6, Virus Definition File 51022u, October 22, 2003).

Aventis Pharmaceuticals Inc. • 200 Crossing Boulevard • PO Box 6890 • Bridgewater, NJ 08807-0890 • www.aventis.com
Telephone (908) 304-7000

This submission consists of the following items, as indicated on the Form FDA 356h:

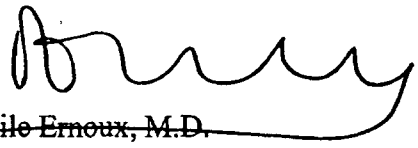
Items as described in Form FDA 356h and their location within the submission		
Item	**Description**	**Folder name**
8	3001 amended report	clinstat
11	Xpt files bgprof/efficacy	crt

Item 8, 3001 amended report (clinstat subfolder): Included with the amended study report is an errata page that both describes all revisions made to the main body of the report and lists the end-of-text tables and figures that have been modified.

Item 11, Xpt files (crt subfolder): 2 SAS Transport Files (BGPROF and EFFICACY), which were affected by inclusion of the initially omitted blood glucose values, have been updated and are included in this submission.

Aventis Pharmaceuticals Inc. looks forward to working with the Division to facilitate the review of the APIDRA™ NDA. Should you have any questions regarding this material, please contact the undersigned by telephone at (908) 231-3536 or by fax at (908) 304-6318 or, in my absence, please contact Steve Caffé, M.D. by telephone at (908) 231-5863.

Sincerely,



~~Odile Ernoux, M.D.~~

Director, Regulatory Affairs
Aventis Pharmaceuticals, Inc.
Phone: (908)-231-3536
Fax: (908)-304-6318

Rhee, H Julie

From: Rhee, H Julie

Sent: Friday, October 17, 2003 9:16 AM

To: 'Michael.Lutz@aventis.com'

Subject: NDA 21-629 Apidra

Hi Michael,

I am sending this additional clinical information request to you since Dr. Ernoux said she is not sure whether or not she has a secured e-mail account with us. Could you please forward this e-mail to Dr. Ernoux?

Thanks,

Julie

NDA 21629 Apidra (insulin glulisine [rDNA origin] for injection)

We are reviewing the Clinical section of your June 18, 2003, submission and have the following comments and information requests. Please provide requested data in both a pdf and MS Word document and submit them to the Electronic Document Room.

Treatment-emergent Adverse Cardiac Events, Cardiovascular History, History of Cardiac Events, and Additional Information Regarding Hypoglycemia and Possible Relation to Emergent Cardiac Events

1. Please submit data of all patients with treatment emergent cardiac adverse events, by study, in a tabular form. Please provide a separate table for each study. Please submit data for all clinical studies, including Studies 3001, 3002, 3004, 3006, 3005, 3100 and 3012. A shell outline with some data from Study 3001 is indicated below as an example.

   The "history of cardiovascular disease" category should include any history of angina, coronary artery disease, myocardial infarction, arrhythmia, or other cardiovascular disease, with dates or patient's age at that time. Please also include any history of hypertension, as well as past or current history of smoking (please quantitate number of cigarettes per day), and lipid profile on entry into study, as well as any antihypertensive and /or antihyperlipidemic medications. Since this category of cardiovascular disease encompasses a lot of information, a separate table may be necessary to include all the cardiovascular-related data for each patient with a treatment emergent cardiac adverse event.

Patient ID	Study Drug	Age/Sex/ Race	Duration of Diabetes Mellitus	History of Cornary Artery Disease	Cardiac Evaluation during study	Categoriz-ation as AE/SAE/WD	Description of cardiac treatment emergent adverse event	Time to onset of cardiac TEAE (i.e. # days after study drug or placebo initiation)	#Episodes of Hypoglyce mia (list serious and non-serious separately) and time of onset for SAE hypoglyce mia	Related to Hypogly cemia	Is TEAE related to drug?
0806/06	glulisine					SAE	coronary artery disease				
0911/11	glulisine					SAE	coronary artery disease				
1202/09	glulisine					SAE	acute myocardial infarction				
1503/02	glulisine					SAE	myocarditis				
1401/05	glulisine					SAE WD	angina pectoris and acute myocardial infarction				

2. Please submit patient profiles and CRFs for all patients with cardiac TEAEs in the different studies, including any additional information regarding the history of cardiac disease in each patient, any cardiac evaluation during the study (e.g., angina, myocardial infarct, arrhythmia, catheterization, angioplasty, stress test, coronary artery bypass graft surgery), time to onset (from baseline drug initiation day) of cardiac TEAE and clinical history of event and outcome.

3. Please submit tables, by study, summarizing the cardiac histories of patients at enrollment.
A sample table shell is outlined below. Please complete for *studies 3001, 3002, 3004, 3006, 3005, 3100 and 3012.

Please define working definition of "cardiac disease."
Please also compare the number of patients on glulisine and comparator - with and without cardiac disease, according to the following three categories (in addition to the list of cardiac treatment emergent adverse effects and episodes of hypglycemia):
(a) hypertension or history of hypertension, at baseline;
(b) current or prior smoking history;
(c) presence of hyperlipidemia, with of presence of LDL > 130 mg/dl, and fasting triglyceride > 180 mg/dl.

Study * [for all studies, separately by study]	Total	# (%) with a History of Cardiac Disease; also indicate % male	# (%) without a History of Cardiac Disease; also indicate % male
#patients screened			
#patients randomized to glulisine			
# patients randomized to comparator (please indicate comparator)			
#patients treated with glulisine with cardiac TEAE			
#patients treated with comparator with cardiac TEAE			
#cardiac TEAE in glulisine-			

treated group			
#cardiac TEAE in comparator -treated group			
#patients treated with glulisine with adverse event(s) of hypoglycemia (please indicate separately for serious and non-serious adverse events)			
# hypoglycemia SAE (glulisine group)			
#patients treated with comparator with adverse event(s) of hypoglycemia (please indicate separately for serious and non-serious adverse events)			
# hypoglycemia (comparator group)			
Baseline hypertension (treated or untreated) or history of hypertension in glulisine group			
Baseline hypertension (treated or untreated) or history of hypertension in comparator group			
Current or prior smoking history in glulisine group			
Current or prior smoking			

history in comparator group			
Baseline LDL > 130 mg/dl In glulisine group and/or treatment for hyperlipidemia			
Baseline LDL > 130 mg/dl In comparator group and/or treatment for hyperlipidemia			
Baseline fasting triglyceride > 180 mg/dl in glulisine group and/or treatment for hypertriglyceridemia			
Baseline fasting triglyceride > 180 mg/dl in comparator group and/or treatment for hypertriglyceridemia			

Rhee, H Julie

From: Rhee, H Julie
Sent: Friday, October 17, 2003 9:18 AM
To: Zawadzki, Joanna K
Subject: FW: NDA 21-629 Apidra

Joanna,

Since I was having such a difficulty trying to format landscape to portrait orientation, I decided to send the document as an e-mail attachment.

Julie

-----Original Message-----
From: Rhee, H Julie
Sent: Friday, October 17, 2003 9:16 AM
To: 'Michael.Lutz@aventis.com'
Subject: NDA 21-629 Apidra

Hi Michael,

I am sending this additional clinical information request to you since Dr. Ernoux said she is not sure whether or not she has a secured e-mail account with us. Could you please forward this e-mail to Dr. Ernoux?

Thanks,

Julie